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In utero exposure to tobacco smoke and subsequent reduced fertility in females

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BACKGROUND: Animal studies have shown that *in utero* exposure to chemicals in tobacco smoke reduces female fertility, but epidemiological findings have been inconsistent.

METHODS: We examined the association between *in utero* exposure to tobacco smoke and female fertility among women in the Norwegian Mother and Child Cohort Study, enrolled from 1999 to 2007. Around the 17th week of pregnancy, participants reported how long they took to conceive (time to pregnancy), and whether their mother smoked while pregnant with the participant. This analysis included 48 319 planned pregnancies among women aged 15–44 years. We estimated fecundability odds ratios (FORs) using a discrete-time survival analysis, adjusting for age, education and adult tobacco smoking.

RESULTS: The adjusted FOR for *in utero* exposure to tobacco smoke among all subjects was 0.96 [95% confidence interval (CI): 0.93, 0.98], among subjects reporting no adult tobacco smoking or passive exposure it was 0.96 (95% CI: 0.93, 0.99) and among subjects reporting adult tobacco smoking or passive exposure it was 0.95 (95% CI: 0.91, 0.99). We performed a probabilistic sensitivity analysis to estimate the effect of exposure and outcome misclassification on the results, and, as expected, the association became more pronounced after taking misclassification into account.

CONCLUSIONS: This large cohort study supports a small-to-modest association between *in utero* exposure to tobacco smoke and reduced fertility.

Key words: tobacco smoking / *in utero* exposure / fertility

Introduction

Smoking is a well-established risk factor for many human health conditions, including impaired reproduction (CDC, 2004a). Women who smoke have an increased risk of subfertility, infertility, pregnancy loss, preterm delivery and of giving birth to an infant who is small-for-gestational age (Augood *et al.*, 1998; Kharrazi *et al.*, 2004; Wilks and Hay, 2004; Triche and Hossain, 2007). About 10–30% of women in western countries smoke during pregnancy (CDC, 2004b; Egebjerg Jensen *et al.*, 2008). The effects of passive smoking on reproductive outcomes are less clear (CDC, 2006). Animal studies, however, have shown that *in utero* exposure to smoking-related chemicals reduces female fertility. For example, mice exposed *in utero* to polycyclic aromatic hydrocarbons had fewer and smaller litters (MacKenzie and Angevine, 1981). In rats, *in utero* exposure to nicotine caused decreased ovarian function and increased time to pregnancy (TTP) (Holloway *et al.*, 2007). Epidemiological studies on the association between a mother's smoking during pregnancy and her daughter's fertility have, however, yielded inconsistent findings, which may in part be related to limited sample size (Baird and Wilcox, 1986; Weinberg *et al.*, 1989; Jensen *et al.*, 1998, 2006; Joffe and Barnes, 2000). To examine the association between a mother's smoking during pregnancy and a daughter's fertility in a large study, we analyzed data from a pregnancy cohort in Norway.

Materials and Methods

The Norwegian Mother and Child Cohort Study

This study is based on the Norwegian Mother and Child Cohort Study (MoBa), conducted by the Norwegian Institute of Public Health (Magnus *et al.*, 2006). Enrollment was from 1999 to 2008 and about 107 000 pregnancies among 90 000 women were included. The present study is based on the 90 190 pregnancies recruited from 1999 to 2007 whose data appeared in the MoBa version 4.201 data set. The majority of all pregnant women in Norway were invited to participate, and the response rate was about 44%. During weeks 17–18 of gestation, participants were asked to complete a questionnaire about demographic characteristics, reproductive health, disease and medication history, lifestyle and socioeconomic status. The Regional Committee for Medical Research and the Norwegian Data Inspectorate approved the study, and informed consent was obtained from each participant.

In utero exposure to tobacco smoking

Women were asked: 'Did your mother smoke when she was pregnant with you?' Women could answer 'yes', 'no' or 'don't know'. Those who answered 'yes' to this question were classified as having been exposed to tobacco smoke while *in utero*; those who responded 'no' were considered unexposed.

Time to pregnancy

TTP is a measure of a couple's ability to conceive with regular intercourse and no use of birth control (Baird *et al.*, 1986). To ascertain TTP, women were first asked: 'Was this pregnancy planned?' Those who planned their pregnancy were further asked: 'How many months did you have regular intercourse without contraception before you became pregnant?' Women could choose one of three response options: 'less than 1 month', '1–2 months' and '3 months or more'. Women choosing the '3 months or more' option were further asked to report the actual number of months. Women were also asked if they had received any infertility treatment in connection with this pregnancy.

Exclusions

As noted above, data for 90 190 pregnancies were available. The selection of the analysis sample with the exclusion criteria is shown in Fig. 1. We restricted our analysis to the woman's first MoBa pregnancy. Women who met at least one of the following criteria were excluded from the primary analysis: (i) age <15 or >44 years old; (ii) reported an unplanned pregnancy (including those who reported contraceptive failures) or did not report this information; (iii) did not report TTP or reported TTP inconsistently (TTP was considered as inconsistent if, for example, a woman reported that she became pregnant within 'less than 1 month' or '1–2 months' but then answered ≥ 3 to the next question ['number of month if more than 3']); and (iv) did not report her mother's smoking when pregnant (question not answered or answered 'don't know') or reported inconsistent information. The reported information on the mother's smoking was considered inconsistent if a woman was enrolled for more than one pregnancy and gave a different answer on two questionnaires. Women with missing values for covariates ($n = 2231$) were excluded from the final data analysis as described below. Overall, 48 319 women met the criteria for inclusion in the primary analysis.

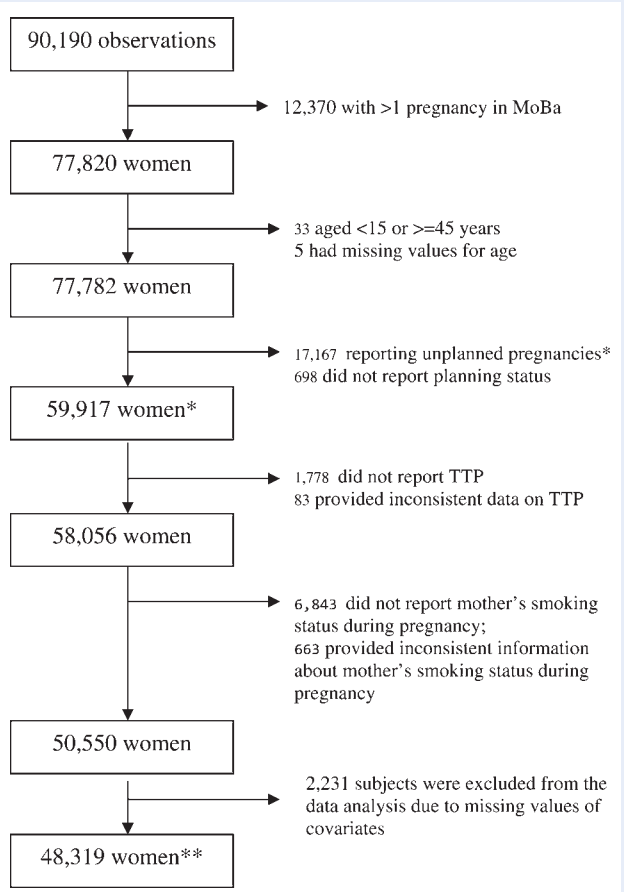

Figure 1 Flowchart for subject selection in the study of the association between *in utero* exposure to tobacco smoke and female fertility among women in the Norwegian Mother and Child Cohort Study (MoBa), enrolled from 1999 to 2007. *Characteristics of these subjects are shown in Table I. **Characteristics of these women are shown in Table II.

Data analysis

To analyze the association between *in utero* exposure to tobacco smoke and TTP, the fecundability odds ratio (FOR) was estimated using the logistic regression analog of discrete-time survival analysis (Abbott, 1985) in Stata/SE (Stata Statistical Software, release 10.0; Statacorp, College Station, TX, USA). An FOR < 1 indicates reduced fecundity. Those who reported 'less than 1 month' were assigned a TTP of 1 (to indicate that they conceived in the first cycle at risk) and those who reported '1–2 months' were assigned a TTP of 2. Those with a TTP of ≥ 3 months were assigned the value corresponding to the reported number of months. Among couples who had been trying to conceive for >12 months, TTP was censored at 13 months because the prevalence of infertility treatment is high in such groups (Boivin *et al.*, 2007), and was 45% in these data. Overall, 11% were censored at 13 months. Women who received infertility treatment for the current pregnancy and became pregnant after fewer than 13 months had their TTP censored at TTP $-$ 1 ($n = 980$).

In the adjusted analysis, *a priori* we included subject's age, education level and adult tobacco smoking status before pregnancy as categorical variables, as shown in Table I. In addition, we evaluated as potential adjustment factors her partner's smoking status (yes versus no), history of sexually transmitted diseases (yes versus no) and chronic diseases before

Table I Characteristics of pregnancy planners and non-planners in the study of the association between *in utero* exposure to tobacco smoke and female fertility among women in the Norwegian Mother and Child Cohort Study, enrolled from 1999 to 2007.[a]

Variable	Planners (n = 59 917)	Non-planners (n = 17 167)
Mother smoked when she was pregnant with the subject (%)[b]		
No	64.5	59.7
Yes	24.0	27.6
Don't know	10.0	10.8
Missing	1.8	1.9
Subject's age at enrollment [mean (SD), years]	29.8 (4.3)	28.4 (5.6)
Subject's age at enrollment (%)		
<20	0.6	5.2
20–24	10.0	21.3
25–29	37.2	30.7
30–34	38.1	27.4
35–39	12.9	12.9
≥40	1.3	2.5
Subject's completed education (%)		
<High school	1.8	6.1
High school	26.7	38.9
College or university	62.1	41.1
Other education	6.4	7.6
Missing	3.1	6.2
Subject's adult tobacco smoking before pregnancy (%)		
None	64.7	48.9
Active smoking only	22.4	30.0
Passive smoking only	5.0	6.4
Both	5.3	11.2
Missing	2.7	3.4

[a]All differences between pregnancy planners and non-planners shown in the table were statistically significant (χ^2 or t-test) at the $P < 0.001$ level. [b]663 women who reported inconsistent information on this item were excluded for this comparison.

Table II Characteristics of planners with and without *in utero* exposure to tobacco smoking.

Variable	*In utero* exposure to tobacco smoking	
	No (n = 35 195)	Yes (n = 13 124)
Time to pregnancy 13 months or more (%)	10.8	12.0
Age at enrollment [mean (SD), years]	30.0 (4.2)	29.6 (4.3)
Age at enrollment (%)		
<20	0.4	0.8
20–24	8.9	11.0
25–29	36.8	37.3
30–34	38.9	38.1
35–39	13.5	11.9
≥40	1.5	0.9
Completed education (%)		
<High school	1.3	2.8
High school	23.5	35.4
College or university	69.3	54.4
Other education	5.9	7.5
Adult tobacco smoking before pregnancy (%)		
None	71.3	56.1
Active smoking only	20.1	28.9
Passive smoking only	4.6	5.9
Both	3.7	9.1

pregnancy (yes versus no). Starting with a model including all *a priori* and potential adjustment factors, we used a backward stepwise elimination algorithm to identify those whose omission changed the FOR for *in utero* smoking by 10% or more (Atashili and Ta, 2007). Elimination of the potential adjustment factors had essentially no effect on the adjusted FOR, and the final model (primary analysis) included only the variables selected *a priori*. We also examined effect modification by the subject's adult tobacco smoking exposure before pregnancy, using likelihood ratio statistics. Effect modification was considered potentially important if the P-value of the likelihood ratio test was <0.1.

We performed a probabilistic sensitivity analysis to evaluate and attempt to correct for bias owing to non-differential misclassification of exposure and outcome (Fox *et al.*, 2005). A description of the specific technical details employed in this sensitivity analysis is given in the Supplementary data. The median and 95% simulation (confidence) interval of the corrected distributions are presented.

We conducted sensitivity analyses that have been recommended to assess the potential effect of biases that can influence the results of retrospective studies of TTP (Weinberg *et al.*, 1994; Olsen *et al.*, 1998; Joffe *et al.*, 2005). We fit a logistic model to evaluate whether contraceptive failure was associated with *in utero* exposure to tobacco smoke (Joffe *et al.*, 2005). We repeated the primary analysis after (i) including non-planners with imputed TTPs of 1, 2, 3 or 4; (ii) excluding all subjects with a TTP of 1 or 2; (iii) censoring TTP at different thresholds (6, 9, 12 and 14 months); (iv) recalculating TTP in terms of menstrual cycles instead of months (restricted to those reporting regular cycles); and (v) after assigning those who were missing data or who reported 'do not know' for *in utero* smoking (13% of the study population) as either exposed or unexposed.

In other sensitivity analyses, we repeated the primary analysis after (i) adjusting for the use of hormonal contraceptives in the past year (in the subset of women with a TTP < 13 months; (ii) adjusting for parity; (iii) adjusting for amount smoked by the mother before pregnancy (non-smoker, <10, 10–20, 20+ cigarettes/day); and (iv) restricting the analysis to the first MoBa pregnancy that was also the woman's first pregnancy.

Finally, beginning with the 59 917 women with planned pregnancies (Fig. 1), we used multiple imputation with chained equations to impute values that were missing for TTP, *in utero* smoking, education and prepregnancy exposure to tobacco (Raghunathan *et al.*, 2007). Adjusted FORs for *in utero* exposure to tobacco smoke based on five imputed data sets were calculated, and the entire procedure was repeated to assess its reliability.

Table III Fecundability odds ratios (FORs) associated with *in utero* exposure to tobacco smoking (yes versus no) before and after probabilistic sensitivity analysis.

Model	Conventional analysis		After analysis accounting for			
			Exposure misclassification		Outcome misclassification	
	FORs[c]	95% CI[c]	FORs	95% CI	FORs	95% CI
Unadjusted model (all subjects, $n = 48\,319$)	0.93	0.91, 0.96	0.90	0.87, 0.93	0.89	0.82, 0.95
Adjusted model[a] (all subjects, $n = 48\,319$)	0.96	0.93, 0.98	0.92	0.88, 0.95	0.89	0.80, 0.94
Adjusted model,[b] stratified by subject's adult tobacco smoking history before pregnancy						
No	0.96	0.93, 0.99	0.94	0.89, 0.98	0.92	0.86, 0.97
Yes	0.95	0.91, 0.99	0.91	0.86, 0.95	0.87	0.74, 0.94

[a]Adjusted for woman's age, completed education level and adult tobacco smoking before pregnancy. [b]Adjusted for woman's age and completed education level. [c]FORs, fecundability odds ratios; CI, confidence interval.

Results

Compared with planners, a higher proportion of non-planners reported *in utero* exposure to tobacco smoke (Table I). Planners tended to be older than those who had not planned their pregnancies. Sixty-two percent of planners had completed college or university, versus 41% among non-planners. A lower proportion of planners (27%) were exposed to active or passive smoking before the pregnancy than non-planners (36%). The two groups did not differ substantially on other variables (data not shown).

Among planners, the proportion with TTP > 12 months was higher among women with *in utero* exposure to tobacco smoke (12%) than in those without (11%) (Table II). The average age in the two groups was similar. Compared with unexposed subjects, women exposed prenatally to tobacco smoke were less likely to have completed college or university, and a higher proportion of them were exposed to active or passive smoking.

The unadjusted FOR for exposure to *in utero* tobacco smoke among all subjects was 0.93 [95% confidence interval (CI): 0.91, 0.96), and the adjusted FOR was 0.96 (95% CI: 0.93, 0.98) (Table III). We saw no effect modification between a subject's adult tobacco smoking history before pregnancy and *in utero* tobacco smoke exposure (likelihood ratio test, $P = 0.65$, 3 degrees of freedom). Regardless of the non-significance of the effect modification test, we stratified the analysis by the subject's adult tobacco smoking before pregnancy (two categories: no adult tobacco exposure, with adult tobacco exposure including passive smoking) because subjects exposed *in utero* had higher proportions of exposure to adult tobacco smoking. The association among those exposed *in utero* but without any adult exposure would be less likely to be biased by residual confounding by adult smoking. The adjusted FORs for those who had no adult tobacco smoking exposure was 0.96 (95% CI: 0.93, 0.99) and for those who had adult tobacco smoking exposure it was 0.95 (95% CI: 0.91, 0.99).

After taking into account exposure misclassification, the FOR for all subjects was 0.92 (95% CI: 0.88, 0.95), for subjects without adult tobacco smoking exposure it was 0.94 (95% CI: 0.89, 0.98) and for subjects who had a history of such exposure it was 0.91 (95% CI: 0.86, 0.95) (Table III). The association also became more pronounced after taking into account outcome (TTP) misclassification.

The odds of contraceptive failure were unrelated to *in utero* exposure to tobacco smoke (data not shown). The association between TTP and *in utero* exposure to tobacco smoking was slightly attenuated when we included non-planners in the analysis [e.g. adjusted FOR = 0.97 (95% CI: 0.95, 0.99), after imputation of non-planners' TTP as 1 month]. The other sensitivity analyses also indicated that the results were robust. For example, the estimated association was virtually the same when we restricted the analyses to first pregnancies (not shown), and when we assigned the 7506 women who provided an uncertain answer about *in utero* exposure to tobacco smoke as exposed or unexposed (data not shown). Using different censoring thresholds or adjusting for additional variables did not change the association (not shown).

Discussion

In the present study, we found a small-to-modest association between *in utero* exposure to tobacco smoke and reduced fertility. As noted earlier, the findings of previous epidemiological studies on the association between *in utero* exposure to tobacco smoke and fertility have been inconsistent (Table IV) (Baird and Wilcox, 1986; Weinberg *et al.*, 1989; Jensen *et al.*, 1998, 2006; Joffe and Barnes, 2000). The reason for the inconsistency remains unclear, although in both of the prospective studies a reduced fecundability was found (Weinberg *et al.*, 1989; Jensen *et al.*, 1998). Although we also found reduced fecundability, the magnitude of the association was small enough that residual confounding could account for it. Once the effect of misclassification was considered, however, the possibility of a true effect was more evident.

As noted earlier, animal studies provide some evidence for mechanisms through which *in utero* exposure to tobacco smoke could cause reduced fertility in females. Prenatal exposure to cigarette smoke or polycyclic aromatic hydrocarbons (important toxicants in cigarette smoke) induced fetal ovarian germ cell loss, resulting in a significant loss of primordial follicles in mice (Vahakangas *et al.*, 1985;

Table IV A summary of epidemiological studies on *in utero* exposure to tobacco smoke and female fertility.

Author	Location	Sample size	Smoking status reporter	TTP data collected	FORs[a,b]	95% CI[b]
Baird and Wilcox (1986)	USA/Minnesota	663	Daughter	R[c], in months	1.0	0.9, 1.2
Weinberg *et al.* (1989)	USA/North Carolina	221	Daughter	P[c], in cycles	0.5	0.4, 0.8
Jensen *et al.* (1998)	Denmark	423	Daughter	P, in cycles	0.64[d]	0.47, 0.87[d]
Joffe and Barnes (2000)	UK	2587	Mother (at the time of delivery)	R, in months	1.02	0.92, 1.13
Jensen *et al.* (2006)	Denmark	1653[e]	Daughter (20%) and mother (80%)	R, in months	0.81	0.65, 1.02
Present study	Norway	48 319	Daughter	R, in months	0.96	0.93 0.98

[a]For early life smoking exposure: yes versus no. [b]FORs, fecundability odds ratios; CI, confidence interval. [c]R, retrospectively; P, prospectively. [d]Weighted average of stratified FORs (0.70 and 0.53) given in their Table 2. [e]Twins.

Matikainen *et al.*, 2002). Prenatal exposure to nicotine resulted in subsequent ovarian dysfunction and increased TTP in adult female rat offspring (Holloway *et al.*, 2006). Furthermore, other toxic components in cigarette smoke may have similar effects (Miller *et al.*, 2004; Rogers, 2008). *In utero* tobacco smoke exposure has recently been associated with earlier age at menopause (Strohsnitter *et al.*, 2008). This finding provides additional support for an adverse effect of *in utero* smoke exposure on female reproduction.

A daughter's report about her mother's smoking status during pregnancy has been previously shown to be reasonably reliable and valid (Sandler and Shore, 1986; Coultas *et al.*, 1989; Sanderson *et al.*, 1998; Simard *et al.*, 2008). Retrospective TTP data have also been shown to be fairly accurate (Zielhuis *et al.*, 1992). The data on the validity of the measures employed suggested that the effect of non-differential misclassification on our results would be modest. The results of the probabilistic sensitivity analysis verified this.

Our additional sensitivity analyses to assess other potential sources of bias (Weinberg *et al.*, 1994; Olsen *et al.*, 1998; Joffe *et al.*, 2005) did not suggest any substantial differences in the associations between *in utero* exposure to smoke and TTP when planning status, infertility treatment history, TTP cutoffs or unknown reports for *in utero* exposure were accounted for, suggesting that the effect of these biases was probably minor in the present study.

Nonetheless, our questionnaire-based study had several limitations. A daughter's reports about her mother's smoking status during pregnancy have not been validated with biomarkers of the mother's tobacco exposure. Some evidence from biomarker-based studies suggests underreporting of smoking during pregnancy (Shipton *et al.*, 2009), and this would attenuate observed associations. We did not have data on the number of cigarettes smoked per day by any subject's mother or information about the subjects' childhood exposure. Studies have shown that most mothers who smoked during pregnancy continued smoking after pregnancy (Weinberg *et al.*, 1989; Simard *et al.*, 2008), suggesting that adjusting for childhood exposure may lessen the association of *in utero* smoke exposure with fertility. On the other hand, the production of oocytes occurs only during fetal life and this may be a critical window of susceptibility (Pryor *et al.*, 2000). Although retrospective reports of TTP are good (Zielhuis *et al.*, 1992), they are not perfect. Furthermore, we cannot rule out the possibility that differential misclassification affected our findings. Finally, selection bias may have occurred owing to the exclusion of sterile women and pregnancies ending before participation (about the 17th week of gestation), possibly causing an underestimation of effect (Weinberg and Wilcox, 2008).

In summary, we observed a small-to-modest association between *in utero* exposure to tobacco smoke and reduced fertility in this large cohort study, and the association was more pronounced after accounting for exposure and outcome misclassification.

Authors' roles

X.Y. participated in the planning of the analysis, analysis and interpretation of the data and drafted and revised the manuscript. O.B. took part in the conception, planning and interpretation of the analysis, and writing of the manuscript. D.B. took part in the interpretation of the analysis and writing of the manuscript. R.S. and K.H. are investigators with the MoBa, and participated in the planning of and conducting this cohort study, and writing of the manuscript. M.E. and L.A.C.U. participated in the interpretation of results and writing of the manuscript. M.P.L. participated in the conception, design and planning of the study, and supervised the data analysis, interpretation of results and preparation and revision of the manuscript. All authors saw and approved the final version of the manuscript.

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

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